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Filed : **October 10, 2000**

REMARKS

Claims 1, 4, 5, 7, 9 and 61 have been amended, Claim 29 has been allowed. Thus, claims 1, 4, 5, 7-9, 29, 60, and 61 remain pending in the present application. Support for the amendments is found in the Specification and claims as filed. Accordingly, the amendments do not constitute addition of new matter. Reconsideration of the application in view of the foregoing amendments and following comments is respectfully requested.

Objection to the Drawings

The Examiner stated that the drawing depicting Figure 2 was not acceptable, because, in both instances, "SEQ ID NO." was misspelled as "SEQ IS NO." Enclosed herewith is a replacement Figure 2 in which appropriate correction has been made. Thus, Applicants respectfully request reconsideration and withdrawal of the objection to the drawings.

Objection to the Specification

The specification was objected to based on an improperly demarcated trademark, specifically "pBlueScriptTM" at page 47, line 19, of the substitute specification. The Office Action states that each letter of a trademark should be capitalized or otherwise demarcated with the appropriate symbol, and accompanied by generic terminology. Appropriate correction has been made via the amendment set forth above. Thus, Applicants respectfully request reconsideration and withdrawal of the objection to the specification.

Rejections under 35 U.S.C. §112, second paragraph

Claims 9 and 61 were rejected as indefinite based on recitation that the polypeptide has "the migration stimulating factor activity of the polypeptide having the amino acid sequence of SEQ ID NO: 2". The Office Action alleges that although claims 9 and 61 depend directly or indirectly on claim 1 which defines the migration stimulation activity of a polypeptide having the amino acid sequence of SEQ ID NO: 2, that claims 9 and 61 do not require such a definition. Claims 9 and 11 as amended recite that migration stimulation factor activity refers to the ability to stimulate adult skin fibroblast migration into a collagen gel.

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In view of these claim amendments, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §112, first paragraph.(written description)

Claims 1, 7, 8, 9, 60 and 61 were rejected as failing to comply with the written description requirement. The Office Action alleges the specification only describes the sequence shown in SEQ ID NO:2, and that polynucleotides having a sequence with at least 90% homology to a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, and having the activities recited in claim 1, would vary substantially in structure. In addition, the Office Action states that neither the nucleic acid molecules encoding the polypeptide of SEQ ID NO: 2 (e.g., the nucleic acid molecule of SEQ ID NO: 3) nor the polypeptide itself are described in sufficient and detailed manner, so as to reasonably be considered representative of the genus as a whole, since there is no disclosure of a substantial structural feature shared by at least most of the polypeptides of the genus. Applicants respectfully disagree with this conclusion.

Contrary to the Examiner's assertions, there is no **substantial variation** within the polynucleotides which fall within the scope of the rejected claims, which recite a polynucleotide having at least 90% homology thereto encoding a polypeptide comprising the amino acid sequence of VSIPPRNLGY (SEQ ID NO: 41), and encoding a polypeptide (1) having at least 30% of the migration stimulation factor activity of a polypeptide having the amino acid sequence of SEQ ID NO:2, wherein migration stimulation factor activity refers to the ability to stimulate adult skin fibroblast migration into collagen gel; and (2) eliciting antibodies that recognize a polypeptide having the amino acid sequence of SEQ ID NO: 2, but do not recognize fibronectin. Thus, in order to satisfy the features recited in claim 1, there cannot be substantial variation among the claimed polynucleotides or the polynucleotides would not fulfill the recited requirements. As such, Applicants were in possession of the common attributes or features of the claimed subject matter.

The rejected claims are similar to those discussed in Example 14 of the written description training materials available on the PTO's website. In example 14, the written description requirement was found to be satisfied for claims directed to polypeptides with 95%

homology to a disclosed sequence that also possessed a recited catalytic activity, where procedures for making variant proteins were routine in the art and the specification provided an assay for detecting the recited catalytic activity of the protein. This disclosure satisfies the written description requirement even though the applicant had disclosed only a single species and had not made any variants. The Guidelines state that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity."

Similarly, the polynucleotides recited in the pending claims also have very high sequence homology to the disclosed sequence and all encode a polypeptide that comprises SEQ ID NO: 41. In addition, all of the polynucleotides recited in the present claims must encode a protein that (1) has at least 30% of the migration stimulation factor activity of a polypeptide having the amino acid sequence of SEQ ID NO:2, wherein migration stimulation factor activity refers to the ability to stimulate adult skin fibroblast migration into a collagen gel; and (2) elicits antibodies that recognize a polypeptide having the amino acid sequence of SEQ ID NO: 2, but do not recognize fibronectin. Thus, the encoded polypeptides all share an epitope sufficient to elicit such antibodies. Because the claimed polynucleotides encode polypeptides having specific structural and functional features, Applicants have satisfied the written description requirement.

In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious....A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants. . . . Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth

between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The court did not require the applicants in *Wallach* to actually make or individually describe all of the vast number of sequences which encode the disclosed sequence. This is in spite of the fact that only a single sequence was disclosed, and the encompassed genus was enormous due to codon degeneracy in the genetic code– even the most skilled artisan could not individually envision the detailed chemical structure of the nucleic acids encompassed by the claimed genus. The Court reasoned that because it is routine to convert between amino acid sequences and nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to place the applicants in possession of the enormous genus of nucleic acids which could encode the sequence.

In view of the amendments and comments provided above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph.(enablement)

Claims 1, 7, 8, 9, 60 and 61 were rejected under 35 U.S.C. §112, first paragraph. The Office Action alleges that the specification, while being enabling for making and using an isolated, recombinant nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, and isolated, recombinant nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO: 3 from nucleotides 57-1982, does not reasonably provide enablement for making and using any of the other polynucleotides encompassed by the pending claims. The Office Action also contends that absent a teaching of which amino acid(s) in SEQ ID NO:2 can be replaced without loss of activity, sufficient guidance is not provided to allow one of ordinary skill in the art to make, and therefore use, the claimed invention. The Examiner's lengthy rejection then cites *In re Wands* and *Ex Parte Forman* in support of the assertion that undue experimentation would be required to practice the claimed invention. In addition, several references are cited in support of the Examiner's position that single amino acid changes can result in significant structural and/or functional differences in the resulting protein.

Although the claims are directed to nucleic acids encompassing many structures, they all share common structural and functional characteristics: 1) they encode a polypeptide

comprising SEQ ID NO: 41; 2) they encode polypeptides having at least 30% of the migration stimulation factor activity of a polypeptide having the amino acid sequence of SEQ ID NO:2, wherein migration stimulation factor activity refers to the ability to stimulate adult skin fibroblast migration into a collagen gel; and 3) they elicit antibodies that recognize a polypeptide having the amino acid sequence of SEQ ID NO: 2, but do not recognize fibronectin. The determination of whether a specific polynucleotide encodes such a polypeptide can be accomplished using the methods described in the present specification, and in the relevant section of the Picardo reference which has been incorporated into the specification. Thus, the present specification teaches that variants of the polypeptide of SEQ ID NO: 3 can be made, and the ability of such a protein to satisfy the present claims can be easily determined using antibody binding and MSF activity protocols provided in the present specification.

The specification teaches in detail how to make and use the claimed polynucleotides, including variants thereof, and antibodies which specifically bind to the resulting polypeptides. Likewise, the specification provides sufficient guidance as to how to use the claimed polynucleotides. Thus, contrary to the Examiner's conclusory statement, there is significant guidance how to make and use the claimed polynucleotides. In addition, as the disclosure and references cited in the specification make clear, the production of polynucleotides, polynucleotide variants, and specific antibodies to polypeptides encoded by the claimed polynucleotides is a predictable and well established aspect of the biological sciences. *See, e.g., In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) (reversing the Board's decision of non-enablement and holding that as of 1980, undue experimentation was not required to make high-affinity monoclonal antibodies to a target peptide).

Since the specification provides ample guidance to one of ordinary skill in the art as to how to determine which polynucleotides would fall within the scope of the present claims, the claims have clearly been enabled. The determination of polynucleotides encompassed by the present claims, although tedious, cannot be considered undue.

In view of the amendments and comments provided above, Applicants respectfully request reconsideration and withdrawal of the §112 enablement rejection.

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Rejection under 35 U.S.C. §102(b)

The Examiner maintained the rejection of claims 1, 7-9 and 60 as being anticipated by WO94/16085 A2. Claim 1 as amended recites, in part, that the polypeptide encoded by the polynucleotide comprises the amino acid sequence of SEQ ID NO: 41. This sequence is neither disclosed nor suggested by the cited reference. Therefore, the reference cannot anticipate claim 1 and any claims dependent thereon.

In view of the claim amendments and comments presented above, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) are respectfully requested.

Rejection under 35 U.S.C. §101

Claims 1, 4, 5 and 7 were rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter. Specifically, the Office Action states that the "recombinant" polypeptides and replicable vectors recited in these claims should be prefaced by "isolated" in order to exclude naturally-occurring products. Appropriate correction has been made.

In view of the claim amendments, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, second paragraph.

Claims 1, 7-9, 60 and 61 were rejected as being indefinite based on recitation of the term "migration stimulation factor". Claim 1 has been amended to refer to the amino acid sequence of "migration stimulating factor" (SEQ ID NO: 2) as suggested by the Examiner.

In view of the amendment to Claim 1, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1, 4, 5 and 7 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while enabling for making and using an isolated, recombinant nucleic acid molecules and isolated replicable vectors, did not reasonably provide enablement for making and using any such non-isolated nucleic acid molecules or replicable vectors. The Examiner stated that it would be remedial to amend claims 1, 4, 5, and 7 to recite "isolated" before "recombinant

polynucleotide" or "replicable vector." Claims 1, 4, 5 and 7 have been amended as suggested by the Examiner, thus obviating this rejection. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph (new matter)

Claims 1, 7-9, 60 and 61 were rejected under 35 U.S.C. §112, first paragraph as containing new matter. Specifically, the recitation of "wherein migration stimulation factor activity refers to ability to stimulate adult skin fibroblast migration into collagen gel" was considered to be new matter. The Examiner acknowledges that although the specification describes assessing the activity of members of a genus of "MSF polypeptides" in "bioassays based in its stimulation of adult skin fibroblast migration, for example, as in Picardo *et al* (1991) *The Lancet* 337, 130-133", but alleges that this disclosure is insufficient to provide proper written support for recitation of "into collagen gel."

The Examiner suggested incorporating relevant portions of Picardo et al. which provide sufficient written support for the present claim language. The specification has been amended to incorporate disclosure relating to collagen gel assay for determining adult skin fibroblast migration. In addition, a declaration stating that the amendatory material consists of the same material incorporated by reference in the referencing material is enclosed herewith. Thus, the recitation of this language in the claims does not represent new matter, and reconsideration and withdrawal of the new matter rejection are respectfully requested.

Rejection under 35 U.S.C. 102(e)

Claims 1, 7-9, 60 and 61 were rejected as being anticipated by U.S. Patent No. 5,830,700, as evidenced by part of the USPTO search report "us-09-581-651d-3.rni" (i.e., Result 2), which was generated by searching the Office's "Issued Patents NA" database using SEQ ID NO: 3 as a query. Claim 1 as amended recites, in part, that the polypeptide encoded by the polynucleotide comprises the amino acid sequence of SEQ ID NO: 41. This sequence is neither disclosed nor suggested by the cited reference. Therefore, the reference cannot anticipate claim 1 and any claims dependent thereon.

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In view of the claim amendments and comments presented above, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(e) are respectfully requested.

Rejection under 35 U.S.C. 102(b)

Claim 9 was rejected under 35 U.S.C. 102(b) as being anticipated by Grey et al. (of record), as evidenced by Schor et al. *(Breast Cancer Res.* 2001; 3:373-379), GenBank™ Accession No. AJ276395. and UniProtKB/Swiss-Prot™ Accession No. P02751. The Examiner states that "a polynucleotide according to claim 1 is not isolated. nor is it necessarily recombinant." (Office Action, page 26). and that "a "recombinant" polynucleotide cannot be distinguished from a naturally occurring nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2...which are found in the cells such as those disclosed by Grey et al."

Claim 9 as amended depends on claim 1 which now recites an **isolated** recombinant polynucleotide. The polynucleotide described by Grey et al. is **naturally-occurring, not isolated**. Thus, there is no anticipation. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 1, 7-9, 60 and 61were rejected under 35 U.S.C. 103(a) as being unpatentable over Grey et al. (of record), as evidenced by Schor et al., GenBank™ Accession No. AJ276395, and UniProtKB/Swiss-Prot™ Accession No. P02751, in view of Bendig (of record). The Examiner alleges that it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have cloned a nucleic acid molecule encoding the polypeptide disclosed by Grey et al. because Grey et al. teaches efforts are underway to do exactly that, and Bending teaches the methodology to do so. Applicants respectfully disagree with this conclusion.

The combination of references set forth by the Examiner do not provide assurance that the correct polynucleotide will be obtained, nor do these references suggest the recited structural detail of the polynucleotide encoding MSF (e.g., encoding the polypeptide of SEQ ID NO: 41).

In re Bell, 991 F.2d 781 (Fed. Cir. 1993) and *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995) are directly analogous to the present claims.

In *Bell*, the prior art disclosed amino acid sequences for insulin-like growth factor ("IGF") polypeptides, as well as general methods for cloning genes (*Id.* at 783). The court held that the claimed invention, directed to specific nucleic acid molecules that encode human IGF, was non-obvious because there are a vast number of nucleic acid molecules that could encode the prior art proteins, and the prior art failed to suggest which of the possible sequences was the human nucleic acid molecule *Id.* at 784.

In *Deuel*, The claimed invention was directed to an isolated nucleic acid molecule encoding heparin-binding growth factors ("HBGF"), proteins found in urine and placental tissue that stimulate cell division and replacement of damaged or diseased tissue. See *id.* at 1554-55. The prior art disclosed the first 19 amino acids of heparin-binding brain mitogens ("HBBM"), proteins found in the brain that are identical for human and bovine, and the prior art also taught general methods of DNA isolation. See *id.* at 1556. The Federal Circuit held that whereas structural relationships may provide the motivation to obtain new compounds by modifying prior art compounds, here, the prior art taught only proteins, not closely related DNA molecules. See *id.* at 1558. In view of the degeneracy of the genetic code, and hence the multitude of DNA molecules that may encode any given protein, knowledge of the protein does not render obvious a particular DNA encoding it. See *id.* at 1558-59. Further, the Court clearly articulated that prior art methods for isolating DNA molecules are "irrelevant" to the obviousness test for DNA molecules thereby obtained. See *id.* at 1559.

Thus, the Federal Circuit has clearly promulgated that the disclosure of a polypeptide sequence does not render obvious the polynucleotide which encodes it. Accordingly, a *prima facie* showing obviousness cannot be maintained.

Even if the polynucleotides disclosed in the cited references were considered to be structurally similar to the claimed polynucleotides, the claimed invention would still be nonobvious because no guidance is provided in the cited references for cloning the correct MSF gene and obtaining its complete sequence. In addition, significant difficulties were encountered in cloning the claimed MSF gene and obtaining its complete sequence which would argue against obviousness. For example:

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A small amount of partial amino acid sequence is given, but this sequence is similar to fibronectin and, in fact, is not present in the MSF which has now been cloned and sequenced in the present work (see below). It is suggested that MSF activity isolated from foetal fibroblast conditioned medium consists of three proteins, one with an apparent molecular weight of 119kDa and a double of 43 and 33lDa, and indeed, it was suggested that MSF could be a proteolytic degradation product of fibronectin. (specification at page 2, lines 12-19)

Further progress in understanding MSF was hindered by the fact that it has not been clear whether MSF is a degradation or breakdown product of fibronectin, and because MSF appears to be structurally related to fibronectin. (specification at page 4, lines 1-4)

In view of the amendments and comments discussed above, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103 (a).

CONCLUSION

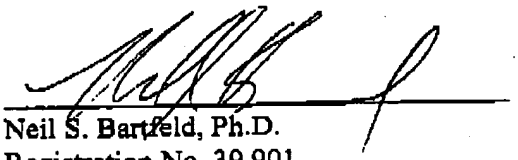
The amended claim set is believed to be in allowable form. Applicants respectfully request that the Examiner contact the undersigned agent should any additional amendments be needed in order to secure allowance of the application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: April 19, 2006

By: 

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